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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,216	12/13/1999	GRAHAM P. ALLAWAY	50875-F-PCT-	2202

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COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/460,216	ALLAWAY ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination was filed on 11 October, 2005, under 37 C.F.R. § 1.114 along with the fee set forth in 37 C.F.R. § 1.17(e). Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 13 June, 2005, has been entered.

Status of the Claims

Claim 61 is pending and claims 1-60 and 62-65 have been canceled without prejudice or disclaimer.

35 U.S.C. § 112, Second Paragraph

Claim 61 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. The reference to an agent that is "capable of binding", "capable of blocking", and "not capable of blocking" fails to adequately set forth the metes and bounds of the patent protection desired because this is a relative term. It is not readily manifest if the agent of interest actually binds to CCR5, blocks HIV-1_{JR-FL}-mediated cell fusion, or fails to block HIV-1_{BRU}-mediated cell fusion. Applicants should amend the claim language in such a manner as to remove the

ambiguity (i.e., said agent binds to CCR5; said agent blocks HIV-1_{JR-FL}-mediated cell fusion; said agent fails to inhibit HIV-1_{BRU}-mediated cell fusion).

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claim 61 stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, (Fed. Cir. 1997). *Fiers v. Revel Co.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, (Fed. Cir. 1993). *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016, (Fed. Cir. 1991). *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, (Fed. Cir. 2002). *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *University of Rochester* v. *G. D. Searle & Co., Inc.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). The claim is directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a $CD4^+$ cell by contacting said cell with an **agent** that is capable of binding to cell surface CCR5. The claim also stipulates that said agent blocks HIV-1_{JR-FL} fusion with a PM-1 cell while not affecting fusion of the

HIV-1_{BRU} with the same cell type.

As previously set forth, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had **possession** of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of **agents** that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, **structures**, figures, diagrams, and **formulas** that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). **The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest.** *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d

1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). **The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.**

An applicant may show possession of an invention by disclosure of drawings or **structural chemical formulas** that are sufficiently detailed to show that applicant was in **possession** of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., **complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.** For some biomolecules, examples of identifying characteristics include a nucleotide or **amino acid sequence, chemical structure, binding affinity,** binding specificity, and molecular weight. **The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function.** Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, **disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement.** *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is

sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claim of the instant application is broadly directed toward **any agent** that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The claims do not limit the genus to any particular type of compound (i.e., peptidyl, organic, fatty acid, etc.) or any particular family of compounds (small molecular weight peptidyl inhibitors, antibody-based reagents, etc.). The disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. This method by itself does not lead the skilled artisan to any particular class of compounds. The disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. Thus the genus corresponding to the agent employed in the claimed assay encompasses an inordinate number of unrelated species (e.g., proteins, oligopeptides, retroinverso oligopeptides, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, small molecule inhibitors, etc.). It is noted that some data was supplied pertaining to a limited number of agents from two subgenuses. Specifically, a small number of β-chemokines were identified with inhibitory activity (e.g., the **β-chemokines MIP-1α** and **-1β**). These two chemokines are natural ligands for the CCR5 receptor. A second group was identified including a small and limited number of **CCR5-specific monoclonal antibodies** (e.g., **PA-9-12**). Appropriate amendment of the claim language to incorporate these two subgenuses would obviate the rejection (i.e., "...contacting the cell with a CCR5-specific monoclonal antibody selected from the group consisting of PA-9, PA-10, PA-11, and PA-

12" or "...contacting the cell with a β-chemokine selected from the group consisting of MIP-1α and -1β").

Although the specification does provide a small number of inhibitory agents, nevertheless, this limited number of species are insufficient to place the inventors in possession of the full genus of agents at the time of filing. First, the disclosure fails to provide any significant structural information concerning the molecular determinants (i.e., epitopes, structural domains, etc.) on CCR5 that modulate CCR5-CD4-gp120 binding events. Thus, the skilled artisan would not be able to perform any type of rational drug-screening approach. Instead, putative antiviral agents would need to be identified through trial-and-error. Second, the disclosure fails to provide adequate guidance pertaining to the structures of any particular subgenus of inhibitory agents. The disclosure fails to provide any useful structural criteria for small molecule inhibitors, peptidomimetics, retroinverso polypeptides, antigen-antibody binding sites, etc. Thus, the skilled artisan cannot readily envisage the structure of any particular putative antiviral agent. Third, although the specification provides a generic screening assay to identify potential candidate molecules, nevertheless, this assay fails to lead the skilled artisan to any particular subgenus of inhibitory agent. Applicants are essentially relying upon others to identify putative antiviral agents that would meet the claim limitations. Fourth, the state-of-the-art as it pertains to HIV antiviral development is characterized by unpredictability. The CCR5 chemokine receptor is a large transmembrane spanning protein. It interacts with both gp120 and CD4 during virion-cell fusion events. These interactions may employ linear domains or conformational domains. However, the precise determinants modulating these binding interactions remain to be elucidated. Accordingly, it would be difficult for the skilled artisan to identify candidate agents because of the dearth of structural information. For instance, if the skilled artisan was employing a peptidomimetic,

what is the appropriate amino acid sequence of said mimetic? If the skilled artisan is going to employ a small molecule organic inhibitor, what is the structure of this compound? The disclosure fails to address these concerns. Accordingly, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed genus of compounds at the time of filing.

Response to Arguments

Applicants traverse the rejection and submit that the pending claim is not directed toward an agent, but rather a method of inhibiting macrophage tropic HIV-1 infection of $CD4^+$ cells, suggesting that the written description criteria relied upon are not applicable in this situation. Applicants are directed toward *University of Rochester* v. *G. D. Searle & Co., Inc.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004), wherein the court concluded that the written description requirement applies equally to both product and method claims. The court unambiguously stated that a "patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound,...,is subject to written description requirement,...,since requirement applies to all inventions, including chemical inventions involving nongenetic materials, and since fact that patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide description of compound sufficient to distinguish infringing methods from noninfringing methods." The facts in this situation are similar to the facts in the instant application. Applicants are claiming a method that employs a poorly defined agent. The agent is described solely in functional terms without any accompanying meaningful structural limitations. The court also noted that "Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the purview of one of ordinary skill in the art in

the 1993-1995 period". Thus, the skilled artisan would reasonably conclude that applicants were not in possession of the full genus of agents at the time of filing.

It was additionally argued that since the level of skill in the art was high, the level of disclosure required to meet the written description requirement is considerably less. The examiner does not concur with this assessment. The effective filing year of the application is 1996. Contrary to applicants' assertion, the design of HIV antiviral agents was a difficult undertaking (Gait and Karn, 1995; Richman, 1996; Mellors, 1996; Back, 1999). As Gait and colleague (1995) conclude, "There can be few tasks in biotechnology that are more challenging than designing antiviral drugs...early protease inhibitors tended to suffer from problems of short serum half-life, poor bioavailability and rapid clearance...new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven tissue distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage." Clearly the generation of efficacious antivirals is not a facile undertaking.

Applicants also argue that since they provided a screening assay for identifying agents with the desired properties, they clearly were in possession of the claimed invention. This argument is also inapposite. As set forth *supra*, the court in *Univ. of Rochester* clearly established that simply providing a generic methodology was insufficient to meet the written description requirement without some significant structural/functional nexus. Simply having a screening assay does not allow the skilled artisan to readily envisage the structure of any given agent with the desired functional properties. The disclosure needs to provide a more detailed structural and functional analysis.

Applicants provide another declaration by Dr. Dragic in support

of their arguments. Dr Dragic argues that the level of skill in the art was very high at the time of filing as evidenced by the disclosed screening assay and identified agents (e.g., β-chemokines and CCR5-specific Mabs) that inhibit macrophage-tropic fusion. Dr. Dragic also argued that a clear correlation was provided between the function and identifying characteristics of the claimed agent. These arguments are clearly not persuasive for the reasons discussed *supra*. First, applicants are reminded that they must be in possession of the claimed invention at the time of filing. Second, the disclosure fails to identify the molecular determinants on CCR5, CD4, and gp120 that mediate binding and virion-cell fusion. This would be useful in helping the skilled artisan identify putative subgenuses of inhibitory compounds. Third, the claims encompass an inordinate number of compounds (i.e., transdominant negative proteins, oligopeptides, peptidomimetics, retroinverso oligopeptides, polyclonal immunological reagents, monoclonal immunological reagents, small molecule organic inhibitors, etc.) which are clearly not disclosed in the specification. Fourth, contrary to Dr. Dragic's assertion, the disclosure fails to provide sufficient guidance pertaining to the structure of these various subgenuses of inhibitory compounds. Perusal of the disclosure would not lead the skilled artisan to any compounds other than those described in the specification. Fifth, although the level of skill in the art at the time of filing was high, so was the unpredictability of the art. The prior art clearly demonstrates that HIV antiviral development is an unpredictable and difficult undertaking. Dr. Dragic's declaration failed to adduce any evidence that would contradict this finding. Finally, the declarant is directed toward the *Univ. of Rochester* decision discussed *supra*. The court clearly established that simply providing a generic methodology was insufficient to meet the written description requirement without some significant structural/functional nexus. The court also noted that "Even with the three-dimensional structures of enzymes such as COX-1 and COX-2

in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the purview of one of ordinary skill in the art in the 1993-1995 period". Thus, the skilled artisan would reasonably conclude that applicants were not in possession of the full genus of agents at the time of filing.

Correspondence

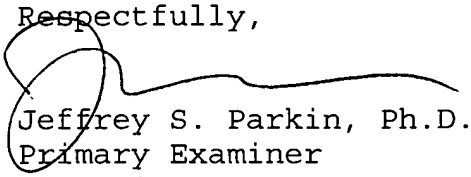
Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access

to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

31 January, 2006

FIG. 9

Anti-CCR5 mAbs Inhibit gp120/CCR5 Binding